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TREATMENT OF HYPERTENSION WITH CHLOROTHIAZIDE

Edward D. Freis, M.D., Washington, D. C.

When chlorothiazide is used, lower and, hence, less toxic dosages of other hypertensive agents become effective in controlling blood pressure. Chlorothiazide does not reduce blood pressure in normotensive subjects, although the drug induces the same increase in salt excretion. Regarding the mechanism of antihypertensive effect of chlorothiazide, it may be tentatively concluded that the blood pressure reduction accompanies the salt loss and probably is a consequence of it. When chlorothiazide is added to the regimen of a patient taking ganglionic blocking agents, the dosage of the latter must be reduced by half. The responsiveness of the patient is so remarkably increased by chlorothiazide that, if full dosage is continued, severe hypotension, including postural collapse, usually will occur. The other so-called toxic reactions to chlorothiazide are only extensions of its fundamental saluretic and kaluretic actions. Hypopotassemia is frequent, and potassium supplements should be used when this develops.

After more than a year of clinical trials, chlorothiazide has become established as a valuable agent for the control of hypertension.[1] It is an especially important drug in general practice, because it can be administered according to straightforward dosage schedules and, in the presence of uncomplicated hypertension, has been relatively free of toxic reactions. Indeed, it has reduced the over-all incidence of toxicity and side-effects of antihypertensive drug therapy. When chlorothiazide is used, lower and, hence, less toxic dosages of other hypertensive agents, such as hydralazine or the ganglion blocking drugs, become effective in controlling blood pressure. The special circumstances under which toxicity can occur will be discussed later.

Mechanism of Effects

Previous reports from this laboratory[2] stressed the importance of salt loss in the mechanism of the antihypertensive effects of the drug. This view has been contested by Wilkins and co-workers.[3] However, further work in this laboratory in the interim has only strengthened the initial observations. These studies may be reviewed briefly here. When chlorothiazide was given to nonedematous, hypertensive

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patients, a urinary loss of approximately 250 mEq. or roughly 1.5 Gm. of salt occurred primarily in the first 24 to 48 hours after the drug was administered. This depletion seemed to be derived in large measure from the extracellular fluid, since measurements of this space disclosed reductions of 1 to 2 liters. Accompanying the diminution in extracellular fluid space was also a reduction in plasma volume (fig. 1). The reduction in plasma volume had also been observed by Tapia and associates.[4] At the same time that these events occurred, the blood pressure fell. It did not precede the saluresis (urinary loss of salt) or follow days later.

These changes were not peculiar to chlorothiazide. They occurred also with ammonium chloride plus mercurials. It is as if well-compensated individuals are, in effect, slightly edematous. At least there seems to be an easily mobilized pool of extracellular fluid which can be skimmed off by saluretic drugs. Another point that leads one to believe that the antihypertensive effect of such agents is secondary to the salt loss is that if sufficient salt is given (and this may require as much as 25 Gm. per day) the antihypertensive effect of the drug is at least partially overcome.

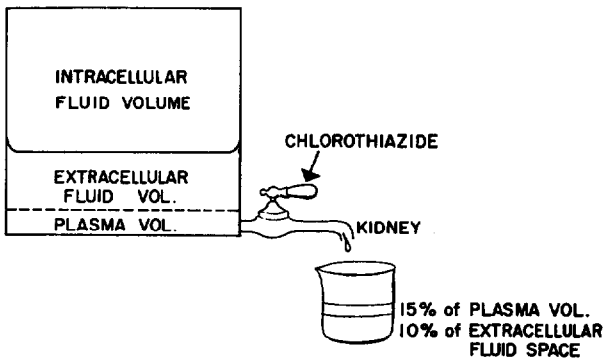

Fig. 1.—Effect of chlorothiazide in nonedematous patients.

Interestingly enough, chlorothiazide does not reduce blood pressure in normotensive subjects, although the drug induces the same increase in salt excretion. However, Dr. A. Wanko, in this laboratory, has shown recently that it changes vascular responsiveness in normal persons even though basal blood pressure is not altered.[5] The pressor response to arterenol is decreased, and the depressor response to ganglionic blocking agents is increased. Most important of all, the vascular responsiveness reverts back to pre-chlorothiazide-therapy levels when the plasma volume is restored with 500 ml. of a 6% solution of dextran.

Dr. I. M. Wilson, also in this laboratory, has carried out repeated determinations of plasma volume and extracellular fluid space in hypertensive patients treated for long periods.[6] She finds that some reduction persists until the drug is withdrawn, after which the volumes rise promptly to pretreatment levels.

At present, therefore, regarding the mechanism of antihypertensive effect of chlorothiazide, it may be tentatively concluded that (1) it has no unique hypotensive properties not shared by other saluretic agents, such as the mercurials; (2) the blood pressure reduction accompanies the salt loss and probably is a consequence of it; (3) the salt loss comes primarily from the extracellular fluid, and the drug produces a sustained reduction of extracellular fluid space and plasma volume; and (4) the reduction of plasma volume and of tissue pressure due to the extracellular fluid loss may play a role in reducing the basal blood pressure of hypertensive but not of normotensive persons and of vascular reactivity in both.

Combined Therapy

It is this increased responsiveness to depressor stimuli that makes chlorothiazide an effective agent in the management of hypertensive patients. By itself, it has only a moderate effect on blood pressure in most patients. But when any type of antihypertensive agent is given in conjunction with chlorothiazide, it gains a new depressor effectiveness. This is particularly true in the case of the ganglionic blocking drugs and of hydralazine (Apresoline) hydrochloride. Because dosages need be less, treatment becomes not only more effective but also simpler, since it is no longer necessary to skirt on the edge of toxic dose levels.

In order for maximum benefit to be obtained from chlorothiazide it must be remembered that hypertensive patients differ in their responsiveness to antihypertensive medicaments. For example, in a random group of 100 hypertensive patients, 20 of those with milder degrees may respond satisfactorily to chlorothiazide alone, 20 others to chlorothiazide and Rauwolfia preparations, and 40 to chlorothiazide and hydralazine, while the final 20 may require the ganglionic blocking drugs, at least for a time. Which of these combinations approaches most closely the ideal of general effectiveness, safety, tolerability, and simplicity? Experience here would indicate that in all forms of mild and moderate hypertension which merit any treatment at all the nearest approach to the ideal is represented by chlorothiazide and hydralazine.

The dosage of chlorothiazide in patients with hypertension uncomplicated by cardiac or renal failure can safely be 500 mg. given twice daily on arising and at bedtime. This will be an effective saluretic dosage in practically all patients, and it avoids the needless complications of titration. In this clinic, patients with uncomplicated hypertension have been given this dosage continuously for

more than one year without toxic effects. To this is added 25 mg. of hydralazine two or three times daily. If this dosage is insufficient, it is raised to 50 mg. three times daily but not beyond this level, since toxic effects can occur at higher dosages. Unlike some other antihypertensive drugs, this combination does not produce easy fatigue, lethargy, or mental dulling. One avoids the considerable danger of precipitating an emotional depression in intellectual persons who are given Rauwolfia, as well as the inconvenience of dosage juggling so frequently required with the ganglionic blocking drugs. Of course Rauwolfia, the ganglionic blocking agents, or both are added whenever the chlorothiazide-hydralazine regimen is ineffective. Dosage readjustments of the blocking drugs are not as frequently required in patients who are also taking chlorothiazide. In addition, the side-effects of ganglionic blockade are far less, due to the lower dosage requirement.

Toxic Reactions

It is necessary at this point to emphasize that, when chlorothiazide is added to the regimen of a patient taking ganglionic blocking agents, the dosage of the latter must be reduced by half. The responsiveness of the patient is so remarkably increased by chlorothiazide that, if full dosage is continued, severe hypotension, including postural collapse, usually will occur. For the same reason, care must be used in administering chlorothiazide to a patient who has previously undergone sympathectomy. This usually is well tolerated, but if such a patient is elderly or has arteriosclerosis there is the possibility of precipitating a coronary or cerebrovascular occlusion if the hypotensive response is marked.

The example just cited could be called a "toxic effect" of chlorothiazide, since the net result is deleterious to the patient. But in a more real sense it is not a failing of the drug, whose purpose is to lower blood pressure, so much as it is a reflection on physicians who proceed thoughtlessly in a situation where wisdom cautions otherwise. The blame in this case is not with the drug but with the physician's judgment.

Similarly, the other so-called toxic reactions to chlorothiazide hold no surprises but are only extensions of its fundamental saluretic and kaluretic actions (fig. 2). The most common of all the "toxic reactions" is hypopotassemia. In patients with uncomplicated hypertension, reductions of serum potassium levels to 3 mEq. per liter is almost commonplace and, in experience at this laboratory, has not been attended by clinical manifestations of hypokalemia or by any evidences of renal damage. The situation in a cardiac patient, on the other hand, has been quite different. Patients with resistant congestive heart failure appear to be potassium "losers," and the addition of chlorothiazide may tip the scale toward critical depletion. This clinical situation is further embarrassed by the fact that digitalis toxicity develops so readily in the presence of hypopotassemia. The first sign of trouble then may be the arrhythmias of digitalis intoxication.

Various measures may be taken to cope with this toxic development. The dosage of digitalis may be reduced or omitted, chlorothiazide may be given intermittently rather than continuously, or potassium supplements may be administered. I do not share the equanimity of other workers regarding the effectiveness of potassium supplements, since they may provide a false sense of security. Chlorothiazide is quite effective in removing excessive sodium in the diet and may do the same with potassium supplements. How much potassium is enough to raise the blood potassium level, and what happens when the patient forgets to take his supplement? These important questions need to be resolved, and it would seem advisable to supply an ample excess of 75 to 100 mEq. orally per day in all patients who develop hypokalemia. There is

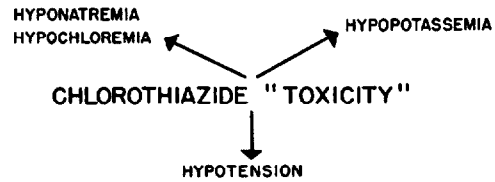

Fig. 2.—Reactions to chlorothiazide as extensions of its fundamental actions.

some evidence to suggest that the hypokalemia may be due to a secondary stimulation of aldosterone secretion.

In the patient who has congestive heart failure secondary to hypertension, it is usually possible to control the failure without digitalis after the blood pressure has been reduced and reaccumulation of edema prevented by chlorothiazide plus other hypotensive agents. There is no need to make a fetish of digitalis if it is harmful in a particular situation. A cautious trial of withdrawal after compensation has been restored will not subject the patient to any significant risk.

In the patient with congestive heart failure due primarily or completely to causes other than hypertension, it is our practice to continue digitalis therapy but to administer chlorothiazide intermittently (usually two days on treatment and two days off), thereby permitting nature to make its own compensations. Unfortunately, in patients with hypertension chlorothiazide must be taken daily, as the blood pressure rises promptly (within 24 to 48 hours) after the drug has been withdrawn.

By the same token, the physician should resist the temptation to give chlorothiazide for correction of hypertension or edema secondary to hyperadrenocorticism, either the naturally occurring varieties or the type induced by steroid treatment. The adrenal cortical hormones conserve sodium and waste potassium. Chlorothiazide increases the excretion of both. In the patient with potassium depletion and hyperadrenocorticism, the additional insult of chlorothiazide may precipitate severe hypokalemia. Similarly, protracted diarrhea, various renal tubular disorders, and ureterosigmoidostomy may in themselves produce potassium depletion and hence make chlorothiazide therapy dangerous. Fortunately, these are situations that rarely arise in the routine management of hypertensive patients.

It is surprising that hyponatremia and hypochloremia do not develop more frequently. There seem to be few authenticated cases, and these conditions have not been observed in this clinic. Once the labile pool of extracellular fluid has been skimmed off, chlorothiazide seems to become relatively ineffective in removing further sodium or chloride. Nevertheless, it would be adding insult to injury to give chlorothiazide in the presence of nephritis with salt loss, or of depletion of body stores of sodium or chloride, as can occur with protracted vomiting or severe diarrhea. On the other hand, last year patients treated with chlorothiazide at this clinic lived through the usual hot Washington summer without any evidences of salt deficiency.

One further word is required on the subject of "toxic reactions" to chlorothiazide. As organic renal damage progresses, the kidney vasculature loses its flexibility in adjusting to a reduced level of blood pressure. When blood pressure falls, glomerular filtration decreases. In the patients with elastic renal blood vessels, adjustments are made quickly so that filtration pressure is restored. But in the rigid vasculature of the patient with far-advanced nephrosclerosis or nephritis, these adjustments are poorly made, with the result that filtration pressure and filtration rate become lower and remain reduced. Such kidneys can ill afford this insult, since they depend on a high urine volume to hold uremia in check. As the filtration rate falls, oliguria develops and nitrogenous products accumulate in the blood.

In the presence of such renal damage and a high level of blood pressure, the physician truly must steer carefully between Scylla and Charybdis. If he aims toward hypotension, he must be aware of the possibility of uremia. But if he withholds therapy, his patient may be drawn further toward malignant hypertension. The only solution then is to proceed cautiously but firmly in the direction of moderating the level of blood pressure, watching scrupulously for oliguria, lightening treatment when this occurs, but pressing forward again watchfully when the danger has passed. Thus, judiciously the physician directs his course altering direction from time to time as prevailing conditions dictate. Few of these patients will be saved even under these circumstances. But the few who are makes the effort worthwhile.

Very often the level of blood urea nitrogen or nonprotein nitrogen will gradually rise. Even in these circumstances, I have persisted for a time, at least, hoping for the occasional instance in which the levels will stabilize and then gradually recede as the patient adjusts to the lower level of blood pressure.

Conclusions

The various complications to chlorothiazide therapy are not common in general practice, but awareness will aid in their prevention. Actually, the good produced by chlorothiazide far outweighs its harm. The discovery of this agent represents a therapeutic advance of considerable significance. The patient with uncomplicated hypertension who does not have congestive heart failure, renal failure, or steroid-induced hypertension has little to fear and much to gain from the use of this drug.

The goal of complete control of elevated blood pressure grows ever nearer. Will this prevent the organic complications that produce morbidity and mortality? I believe it will, but only time and thoughtfully planned studies will provide the final answer.

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